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NEUROTRANSMISSION

Widening exocytosis

α-Synuclein is implicated in the pathogenesis of Parkinson disease (PD), but the physiological function of this protein has been unclear. Now, Edwards and colleagues show that α-synuclein has a role in promoting the dilation of vesicular fusion pores.

Previous studies have found that α-synuclein localizes to nerve terminals and, when overexpressed, inhibits regulated exocytosis of synaptic and large dense-core vesicles (LDCVs), suggesting it has a role in neurotransmission. However, studies involving mice lacking multiple synucleins, including α-synuclein, have provided mixed evidence for such a role.

Here, the authors examined how human α-synuclein overexpression or genetic ablation of all three synucleins affected exocytotic events in adrenal chromaffin cells, which contain LDCVs, and neurons. To do so, they tracked changes in the fluorescence signal generated by the exocytotic vesicle-mediated release of neuropeptides fused to pH-sensitive fluorescent reporters that were virally expressed in these cells. This signal was quenched in LDVCs and synaptic vesicles owing to the low pH found in these structures but increased during exocytosis when the contents of the vesicles became exposed to the extracellular solution, which was at a higher pH. As the peptides dispersed, the signal decayed.

In chromaffin cells, α-synuclein overexpression was associated with a decrease in the number of exocytotic events following K^+-induced depolarization. Moreover, these cells exhibited increases in the time to peak fluorescence and the rate of fluorescence decay for exocytotic events — indicative of increases in the rates of vesicle pore opening and peptide release, respectively. Following depolarization in neurons, α-synuclein overexpression similarly increased the kinetics of exocytotic events. Interestingly, in neurons, overexpressed α-synuclein also decreased the proportion of exocytotic events that were not accessible to extracellular fluid, suggesting that α-synuclein promotes vesicular fusion pore dilation independently of its effects on event kinetics.

In line with the findings described above, chromaffin cells and neurons from mice lacking all three synucleins exhibited prolonged release kinetics. Moreover, such neurons showed an increase in the proportion of vesicles that underwent pore closure. Thus, these data suggest that, like overexpressed α-synuclein, endogenous α-synuclein promotes fusion pore dilation and exocytosis.

Finally, the authors examined the effect of two PD-associated mutant variants of α-synuclein on exocytosis. Similar to overexpressed wild-type α-synuclein, the overexpressed mutant variants of α-synuclein reduced the number of exocytotic events in chromaffin cells. However, the mutants did not accelerate the release kinetics of individual events. This indicates that the effects of overexpressed α-synuclein are dissociable and that these mutations selectively impair pore dilation.

This study shows that α-synuclein promotes dilation of the vesicle fusion pore during exocytosis and that some PD-associated mutations impair this property of the protein.

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> “Following depolarization in neurons, α-synuclein overexpression similarly increased the kinetics of exocytotic events.”